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Study Design Choices for Evaluating Comparative Safety of Diabetic Medications: An Evaluation of Pioglitazone and Bladder Cancer Risk Among Older US Adults with Type-2 Diabetes

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Abstract

Aim.—Empirically demonstrates the effect of varying study design choices to evaluate the safety of pioglitazone on bladder cancer.

Methods.—We identified Medicare beneficiaries aged >65 with diabetes between 2008 and 2015 and classified exposure (≥2 claims within 180 days) to glucose-lowering drugs (GLD; pioglitazone or other). The effects of varying the following study design parameters on bladder cancer risk were assessed - new versus existing drug use, choice of referent (all non-users and users of GLDs, non-insulin GLDs, and DPP-4's), and whether or not censoring accounted for treatment change. We used Cox proportional hazards models to obtain adjusted HRs and 95% CI.

Results.—We included 1,510,212 patients classified as pioglitazone users (N=135,188) or non-users (N=1,375,024). Users had more diabetic complications than non-users, but less than insulin users. The HR ranged from 1.10(1.01–1.20) to 1.13(0.99–1.29) when censoring ignored treatment changes, suggesting weak or no association between pioglitazone and bladder cancer, likely under-estimating risk, but was 1.20(1.01–1.42) when cohorts restricted to new users, censored upon treatment change, and used DPP-4 as the referent, suggesting an increased risk of bladder cancer associated with pioglitazone.

Conclusions.—The continued demand for new GLDs compels the need for more robust observational methods to improve the value of the RWE generation in order to equip clinicians to make informed prescribing decisions. Although there is no one-size-fits-all approach, we

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Contribution statement

E.M.G., J. B. B., J.L.L., M.G., M.E.N., and T.S. participated in study conception and design; E.M.G. drafted the manuscript and analyzed the data with programming support from V.P.; All authors participated in the analysis plan, interpretation of the data, and reviewed and provided comments on the manuscript. E.M.G. is the guarantor of this work; E. M. G. and V. P. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

recommend active comparator new user study designs that compare therapeutically equivalent drugs and account for treatment changes during follow-up to present the least biased comparative safety estimates.

Introduction.

Diabetes affects at least one in five older adults (age ≥65) in the US and over 86% of older adults with diabetes will require treatment with one or more glucose-lowering drug (GLD).[1] The continued demand for new GLDs compels the need for robust observational methods to improve the value of real-world evidence (RWE) and better understand their comparative effectiveness and safety. The safety of the pioglitazone, a GLD from the thiazolidinedione (TZD) class, has been debated for over twenty years despite being generally well-tolerated.[2] The Food and Drug Administration (FDA) issued a safety warning that TZDs may increase and/or exacerbate heart failure in 2007.[3] This was followed by a safety warning in 2011 that exposure more than two years to pioglitazone may increase the risk of bladder cancer,[4] a warning that was later re-issued in December 2016.[5]

Several studies have reported on the safety of pioglitazone; many reported no evidence to suggest an increased risk of bladder cancer associated with pioglitazone use,[6–14] while others reported an increased risk.[15–19] The safety estimates of these studies varied widely. This is likely driven by the different study design choices, which obscures the association between pioglitazone and bladder cancer and makes it difficult to determine the actual safety. The majority of observational studies evaluating this association included all users of pioglitazone without requiring new use;[6–8,11,12,17,20–26] most of which did not report evidence of an increased risk of bladder cancer. Very few studies compared pioglitazone to a single drug (or class of drugs).[9,19,27] Many studies identified all diabetic patients and then compared patients treated with pioglitazone to one composite referent group of all non-users of pioglitazone. While some restricted the composite referent group to patients treated with a GLD[7,11,17,21] or a non-insulin GLD (NIGLD)[10,16,18] other than pioglitazone, many included both those treated and untreated with a GLD.[6,8,12,20,22,23,25,26] Among the comparisons with referent groups that additionally included untreated patients, reports of no evidence to suggest an increased risk of bladder cancer was common, whereas estimates from comparisons to treated GLD or NIGLD referent groups had more variation. Few studies accounted for exposure duration[6,11,17–20,26] and only two studies that we reviewed censored follow-up based on treatment change in addition to outcome, death, or end of study.[17,19] Few studies lagged the exposure period to allow for a sufficient time for development and detection of malignancy (i.e. latency period), excluding outcomes that occur immediately after start of treatment.[16–19] Studies that accounted for exposure changes or lag/latency tended to identify effect estimates furthest from the null, commonly reporting an increased risk of bladder cancer.

Using the example of pioglitazone and bladder cancer among older adults, we sought to understand the impact of heterogeneity of study design on studies evaluating safety of diabetic medications. This paper aims to demonstrate the importance of *how* exposure is defined, *what* exposure is being compared to, and *when* to identify safety endpoints. We varied new versus existing drug use, the choice of the referent group (all non-pioglitazone

patients; users of all GLDs other than pioglitazone; users of all NIGLDs other than pioglitazone; and users of dipeptidyl peptidase-4 [DPP-4] inhibitors), and whether or not follow-up is censored according to treatment change.

Methods

Data Source.

Data was abstracted from a 20% random sample of Medicare Parts A (inpatient), B (outpatient) and D (prescription) adjudicated claims data from January 1, 2007 (start of available data) to December 31, 2015 (end of available data). Medicare provides public insurance to over 98% of older US adults, and contains information about demographic and enrollment characteristics, diagnoses, procedures, and dispensed prescriptions for enrollees.[28] Within Medicare Parts A and B, all diagnoses for medical conditions are recorded via ICD-9 codes on or prior to September 30, 2015 and via ICD-10 codes after. All procedures are recorded via Current Procedural Terminology, Fourth edition (CPT-4) or Healthcare Common Procedure Coding System (HCPCS) codes. Within Medicare Part D, claims for prescriptions dispensed are recorded via National Drug Codes (NDC).

Study Population.

In the 10-year safety study requested by the FDA, patients were selected from a diabetic registry and exposure was assigned hierarchically according to the first group that they qualified for during the cohort entry period without regard to treatment change.[6] Before creating our varied referent groups, we attempted to mimic this design by selecting a cohort of patients with a diabetes diagnosis (ICD-9-CM: 250.x; 2 outpatient claims within 365 days or 1 inpatient claim) with at least 365 days of continuous enrollment with medical and prescription coverage prior to the first inpatient or second outpatient claim.

Exposure.

We identified GLD exposure based on a prescription claim for any GLD between January 2008 and September 2015 with an NDC corresponding to an anatomical therapeutic chemical (ATC) classification system code starting with A10*[29] and classified exposure according to pioglitazone or each of the non-TZD GLD classes (Table S1). Additional detail describing exposure can be found in the e-supplement. New use of GLD exposure was determined based on no prescription claims for the drug classes included in each comparison during the 365-day period prior to the initial claim. Each patient was then hierarchically assigned to one of four mutually exclusive exposure categories: Pioglitazone (≥2 claims within 180 days), GLD (≥2 claims within 180 days), Single GLD (only 1 GLD claim), or Untreated (no GLD claims). Cohort entry was defined according to the first qualifying claim (e.g. second if 2 required; date of diabetes claim for untreated; Figure S2). Patients aged less than 66 upon cohort entry or with a diagnosis of prevalent bladder cancer or common bladder cancer treatment procedures (Table S2) were excluded.

We then created our four varied referent groups to compare pioglitazone users to: all non-users of pioglitazone, GLD users, non-insulin GLD (NIGLD) users, and DPP-4 users (Table S3). We also explored some of the components of the non-pioglitazone composite referent

group thought to be most influential (Table S4). All-user cohorts included all patients according to first qualifying referent group, and new-user cohorts included patients classified according to first new-user referent group that they qualify for during the cohort entry period.

Outcome.

Incident bladder cancer events were defined using an algorithm previously validated for other solid tumors in Medicare data, at least two diagnostic claims for bladder cancer within 60 days.[30] We included carcinoma in situ of the bladder (ICD-9: 233.7; ICD10: D09.0) in addition to all other bladder cancer (ICD-9: 188.x; ICD-10: C67.x, C79.11) diagnosis codes since the majority of bladder cancers are diagnosed at an early stage.[31] The first claim date defined the event date, as thought to be closest to date of actual diagnosis.

Follow-up.

The follow-up period for identifying bladder cancer events was lagged to begin 180 days after the cohort entry date to allow for time between exposure and development of disease (induction period). By excluding cases immediately following exposure, we thereby reduce the potential for spurious associations attributable to increased medicalization after start of a therapy or the possibility of preclinical symptoms of bladder cancer influencing treatment choice (protopathic bias). Patients who died or had the outcome within the first 180 days of follow-up were excluded from the analytic cohort. We compared two censoring approaches. First, an “as-treated” (AT) approach that continued until first occurrence of incident bladder cancer, death, disenrollment of medical or prescription coverage, study end (December 2015), or treatment discontinuation (no subsequent dispensing for initiated drug class within days-supply plus a 90-day grace period). An additional 6-month latency period was also added after treatment discontinuation to allow time for disease manifestation and detection. The second approach, referred to here as the “initial-treatment” (IT) approach, did not censor on treatment discontinuation, similar to the intent-to-treat approach used in randomized controlled trials. Although lag periods are typically applied following new use, we used the same lag period for the all user comparisons to be consistent. Given that pioglitazone was on the market longer than some of the newer drugs, such as DPP-4s and SGLT-2s, follow-up was truncated at 5 years. We analyzed overall follow-up and follow-up stratified at two years, based on the original FDA safety warning. Only the subset of patients not otherwise censored within two years were included in analyses evaluating associations two years after cohort entry.

Statistical Analysis and Confounding Control.

The baseline covariate assessment period prior to cohort entry was 1 year (365 days). Covariates were selected *a priori* to include demographics (age, sex, and race), year of cohort entry, diabetes-related complications (nephropathy, neuropathy, retinopathy), smoking, comorbidities, and use of GLDs and other medications of interest. We used descriptive statistics to summarize covariates and to describe baseline differences across comparisons. The crude bladder cancer incidence rates (first event per patient) were calculated based on the Poisson distribution overall and for each treatment category. Cox proportional hazards models were used to estimate the HRs and 95% CI for incident bladder

cancer. Crude models included treatment as the only independent variable. Partially adjusted models included treatment, age, sex, race, and age-squared as independent variables. To be consistent with the 10-year safety study requested by the FDA,[6] multivariable outcome regression models were used to obtain fully adjusted HRs. All data were analyzed using SAS, v9.4. The University of North Carolina at Chapel Hill institutional review board approved this study.

Results.

Distribution of Patient Characteristics.

Among the 1,510,212 patients who met the entry criteria for diabetes diagnosis, 135,188 were assigned to the pioglitazone Category 1 and 828,527 to the GLD Category 2 (Figure 1). Of the remaining patients, 124,100 had some GLD exposure (Category 3) and 422,397 were untreated. A more detailed summary of the cohort and analytic cohort attrition for all comparisons can be found in Supplemental Table S5. Among the all-user (Table 1) and new-user (Table 2) comparisons, pioglitazone users were generally younger, but no appreciable difference in sex and race. Pioglitazone users were less likely to have a smoking-related claim, congestive heart failure (CHF) and prior use of loop diuretics. There were no clinically meaningful differences in urinary tract-related comorbidities across all comparisons. Other comorbidities were similar for GLD and NIGLD comparisons, but less prevalent in pioglitazone users. In the all-user comparisons, pioglitazone users were generally more likely to have prior NIGLD use and diabetic complications. These differences were more pronounced when pioglitazone was compared to the non-pioglitazone group and for all new-user comparisons, but characteristics were similar when compared to DPP-4 in the new-user comparison.

Incidence of Bladder Cancer.

Figure 2 illustrates the fully adjusted HRs for pioglitazone users compared to each referent group. Additional detail about the number of bladder cancer events and incidence rates per 100,000 person-years, crude HRs, and HRs partially-adjusted for age, sex, and race are reported in Tables S6–S8. Overall, the incidence rates were fairly constant across all analyses ranging from 193.0–230.3 per 100,000 person-years among the all-user comparisons and 188.6–251.0 per 100,000 person-years in the new-user comparisons, with the highest rates highest rates observed in the AT analysis. Given minimal differences in age, sex, and race across all comparisons, partially-adjusted HRs were generally similar to crude. When follow-up did not account for treatment changes, the HR ranged from 1.10(1.01–1.20) to 1.13(0.99–1.29). When cohorts restricted to new users, follow-up accounted for treatment changes, and DPP-4 was used as the referent, the HR was 1.20(1.01–1.42). When follow-up was truncated at 2 years, the HRs increased, the greatest increase identified among the IT analyses. For follow-up after 2 years, there was a late-stage effect and a large increase in variance for all AT analyses as diabetic patients were less likely to stay on the same treatment for long durations, and HRs were generally attenuated for all comparisons except for pioglitazone versus DPP-4, where the HR became larger.

Exploration of the Components of the Non-pioglitazone Composite Referent Group.

When we looked at some of the components of the non-pioglitazone referent group individually (Table S9 and S10), the untreated patients represented 31% of the all-user and 62% of the new-user composite non-pioglitazone referent groups. Long-acting insulin users were more likely to have diabetic complications than pioglitazone users, metformin users, and the untreated, respectively. New users of metformin were younger than new users of pioglitazone, new users of long-acting insulin, and the untreated, respectively. Other comorbidities were highest among the untreated and long-acting insulin groups. Bladder cancer rates for the non-pioglitazone referent group (193.8–195.9 per 100,000 person-years) were similar to its untreated component (196.8 per 100,000 person-years), and higher than its metformin component (174.5–178.9 per 100,000 person-years). (Table S13–S15) Fully-adjusted HRs for pioglitazone versus untreated were similar to pioglitazone versus the overall composite non-pioglitazone referent group; these HRs were higher when compared to metformin and highest when compared to long-acting insulin.

Discussion.

Using the example of pioglitazone and bladder cancer among older adults, this paper highlights how effect estimates can change due to variation of study design choices. Although there are many publications outlining the importance of study design choices, including but not limited to those advocating for the active-comparator and new user designs,[32–36] this paper is the first to systematically vary study design to compare effect estimates when evaluating the safety of a diabetic medication. Similar to the trends we identified in the existing literature on the association between pioglitazone and bladder cancer and as previously suggested,[32,33] we found that estimates were generally lower when all users were included and when treatment changes were ignored, suggesting no increased risk. The HRs increased to 1.20(1.01–1.42) for the new-user comparison to a clinically meaningful treatment alternative, DPP-4, when follow-up accounted for treatment changes. Important differences were identified within the composite referent group of all non-pioglitazone patients indicating that long-acting insulin users were at different stages of diabetic severity than pioglitazone users, metformin users, and the untreated, respectively.

There are many reasons for variation of published estimates. When we plotted the log of all relative estimates of the previously published studies against the precision of each study (Figure S1), we identified an asymmetrical pattern, which may be attributable to publication bias or selective outcome reporting, but is most likely due to the heterogeneity of study design choices.[37] When studies do not restrict to new users of index treatment(s), estimates may adjust for variables affected by prior treatment, which can bias estimation of treatment effects toward the null and under-estimate harm.[32,33] Timing of outcome ascertainment is important especially for cancer outcomes given that the actual risk period relevant for drug-associated cancers is poorly understood.[38] When treatment is defined at baseline ignoring treatment changes that occur during follow-up, estimates are more susceptible to exposure misclassification (via non-adherence), which can attenuate results towards the null, potentially masking drug effects on safety outcomes. Lastly, referent choice can also influence both the interpretation and generalizability of comparative safety estimates,

because confounding by severity threatens study validity when there are major differences in disease severity between those prescribed the exposure and the referent.[34]

Many of the published studies that evaluated the association between pioglitazone and bladder cancer used a composite referent group of all non-pioglitazone. Therefore, we chose to include composite referent groups in this example to empirically demonstrate the impact of this approach on the effect estimates. Although the inclusion of *all* non-users of the drug of interest in a referent group may increase power, effect estimates can be threatened by confounding by disease severity if there are major differences in disease severity between the drug of interest and the composite referent or its components.[34,35] Furthermore, including untreated patients in the referent group can threaten validity further due to confounding by indication, since these patients are inherently different, especially if they either have less severe diabetes and are able to manage their diabetes without medical therapy (e.g., diet and exercise). As expected, the relative risk of bladder cancer for pioglitazone users compared to patients who entered the composite non-pioglitazone group as metformin users was greater than that of pioglitazone compared to the entire non-pioglitazone referent group, because metformin is generally given at the earliest stage of diabetes severity per American Diabetes Association recommendation.[39] We had expected there to be a decreased risk of bladder cancer when pioglitazone users were compared to the long-acting insulin users, given previous literature[9] and the increased frequency of diabetic complications among long-acting insulin users. However, the long-acting insulin users in our sample were at decreased risk of bladder cancer. This is likely due to increased competing risk of death as they experienced differentially more deaths within the first 180 days after cohort entry. (Table S5)

This study used a hierarchical exposure classification as was done previously,[6] searching the entire study period of interest to first identify pioglitazone users, then subsequently identifying other GLD use among those without use of the GLD of interest, and then lastly identifying untreated based on no occurrence of treatment during the entire period. The benefit of this design is that all pioglitazone users are included in the primary exposure group. However, looking into the future to determine cohort entry may impose immortal person-time bias if there are patients who enter the pioglitazone group after treatment with another GLD that are subsequently excluded due to prevalent bladder cancer that may be attributed to the other treatment.[40,41] In this example, the majority of patients classified as pioglitazone users in the all-user comparison had prior exposure to another GLD (Table 1), and ~1% of pioglitazone users with prior GLD use were excluded due to prevalent bladder cancer. Therefore, the hierarchical design excluded bladder cancer cases attributable to the other GLD, lowering the incidence rate among the referent group.

This study has limitations that should be considered when interpreting results. First, although many of the design choices were implemented to be comparable to the 10-year safety study requested by the FDA,[6] we were not able to completely emulate the previous study without a diabetic registry or 10 years of follow-up, among other data differences. Second, we did not have access to pathological confirmation of the bladder cancer outcome defined using claims. However, we used an algorithm previously validated for other solid tumors,[30] and although we acknowledge potential misclassification, it is unlikely to be

differential between treatment groups. Third, we did not have clinical records or biomarkers (e.g. HbA1c) necessary to determine diabetic severity, but evaluated codes for diabetic complications indicative of diabetic severity (neuropathy, nephropathy, and retinopathy) and adjusted for these. The new-user comparisons that included multiple treatments had a substantial loss of power, but measured key covariates were balanced by design across treatment groups, also increasing the confidence about the balance of unmeasured covariates. Given that pioglitazone is often prescribed as second or in some cases third-line therapy, excluding prior use of any GLD among pioglitazone users excluded up to 96% of pioglitazone users, which increased the variance of the estimates. Excluding prior use of metformin excluded more than 50% of pioglitazone users. Fourth, under-report of medication use due to out-of-pocket purchases is possible, but assumed to be minimal. Fifth, a potential for detection bias has been suggested if pioglitazone users receive more urological work-up.[42] However, since urinary tract-related comorbidities were similar across all comparisons, we do not suspect differentially more urological work-up among pioglitazone users. Furthermore, we previously evaluated the rate of urologic diagnostic procedures and found no differences in initiators of pioglitazone compared with initiators of DPP-4s or sulfonylureas.[19] Lastly, to allow comparison with previously reported estimates, we only report relative estimates. Given that the incidence of bladder cancer is low, absolute risks are consistently small requiring almost 2,000 person-years of exposure to see one excess case of bladder cancer among new users of pioglitazone versus DPP-4. Therefore, relative risks may over-report actual harm.

Studies that exclude prevalent users and compare the initiation of the drug exposure of interest to the initiation of a clinically meaningful treatment alternative have been recommended for comparative effectiveness research to present the least biased comparison.[34–36,43] If a composite referent group is necessary due to power concerns, we caution against inclusion of metformin monotherapy users, long-acting insulin users, and untreated diabetic patients. In our example, the DPP-4 initiators were selected as the optimal comparator for pioglitazone initiators since DPP-4s are prescribed to patients similar to those prescribed pioglitazone.[19,44] Although an approach that ignores treatment changes may be added, as-treated estimates should be considered to minimize exposure misclassification for safety estimates. If there is reason to consider follow-up after end of exposure to allow for disease manifestation and diagnosis, such as with cancer outcomes, a latency period can be added to extend follow-up as necessary after treatment changes[45].

Our study empirically demonstrates the effect of varying key parameters when evaluating the safety of diabetes drugs. The continued demand for new GLDs compels the need for more robust observational methods to improve the value of the RWE generation in order to equip clinicians to make informed prescribing decisions. Although there is no one-size-fits-all approach and recommendations may depend on the data source and the research question, we recommend that researchers consider *how* they define exposure, *what* they compare exposure to, and *when* they identify safety endpoints, as these methodological decisions may impact the interpretation of estimates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Duality of interest

E. M. G. was a doctoral student at the University of North Carolina at Chapel Hill, receiving a Graduate Research Assistant stipend from the CER Strategic Initiative of UNC's Clinical & Translational Science Award (UL1TR002489) while implementing this study. She is now a full-time employee of Aetion, Inc. a software and data analytics company, of which she holds stock options. J. B. B. is supported by the NIH (UL1TR002489); JBB has received contracted consulting fees, paid to his institution, and travel support from Adocia, AstraZeneca, Eli Lilly, MannKind, NovaTarg, Novo Nordisk, Senseonics, and vTv Therapeutics and grant support from Novo Nordisk, Sanofi, and vTv Therapeutics' JBB is a consultant to Neurimmune AG; JBB holds stock options in Mellitus Health, PhaseBio and Stability Health. M.G. is a full time employee of GlaxosmithKline and owns GSK stocks. J. L. L. is funded by the UNC Oncology Clinical Translational Research Training Program (5K12CA120780) and receives salary support and research support from the PhRMA Foundation for a Research Starter Award to the Department of Epidemiology, University of North Carolina-Chapel Hill; M.E.N. is supported by the NIH (R01NR016990, R21CA212516) and PCORI (1503-29220); MEN has received consulting fees from the American College of Physicians High Value Care Task Force; MEN holds stock options in Grand Rounds. V.P. receives salary support from investigator-initiated grants from Merck and Amgen and from the Comparative Effectiveness Research (CER) Strategic Initiative, NC TraCS Institute, UNC Clinical and Translational Science Award (UL1TR002489); T. S. receives investigator-initiated research funding and support as Principal Investigator (AG056479) from the National Institute on Aging (NIA), and as Co-Investigator (R01 CA174453; R01 HL118255, R21-HD080214), National Institutes of Health (NIH). He also receives salary support as Director of the Comparative Effectiveness Research (CER) Strategic Initiative, NC TraCS Institute, UNC Clinical and Translational Science Award (UL1TR002489), from the Center for Pharmacoepidemiology (current members: GlaxoSmithKline, UCB BioSciences, Merck, Shire), and research support from pharmaceutical companies (Amgen, AstraZeneca) to the Department of Epidemiology, University of North Carolina at Chapel Hill. Dr. Stürmer does not accept personal compensation of any kind from any pharmaceutical company. He owns stock in Novartis, Roche, BASF, AstraZeneca, and Novo Nordisk.

Abbreviations.

AT	As-Treated censoring approach
ATC	Anatomical Therapeutic Chemical classification system
CHF	Congestive Heart Failure
CPT-4	Current Procedural Terminology, Fourth edition
DPP-4	Dipeptidyl Peptidase-4 inhibitors
FDA	Food and Drug Administration
GLD	Glucose-Lowering Drug
HCPCS	Healthcare Common Procedure Coding System

IT	Initial-Treatment censoring approach
NDC	National Drug Codes
NIGLD	Non-Insulin Glucose-Lowering Drug
SGLT-2	Sodium-GLucose co-Transporter-2 inhibitors
TZD	Thiazolidinedione

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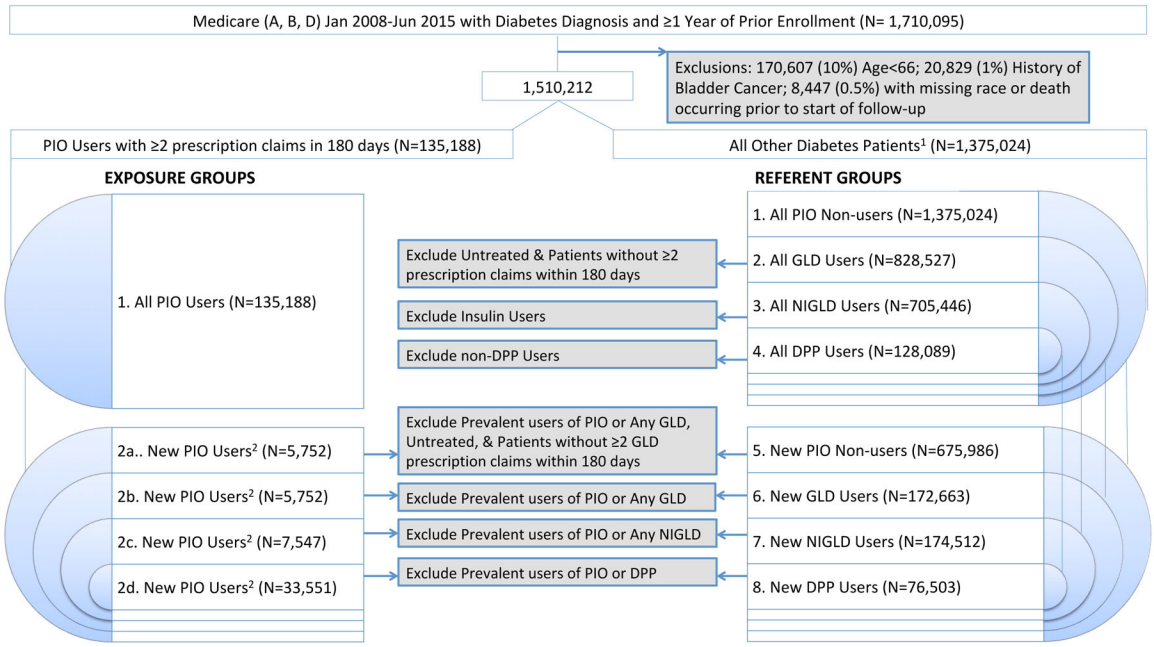

Figure 1. Study flowchart showing cohorts varying referent choice and whether or not restricted to new users

DPP, dipeptidyl-peptidase-4; GLD, Glucose-Lowering Drug; NIGLD, Non-Insulin Glucose-Lowering Drug; PIO, pioglitazone

1. PIO users that did not have ≥2 RX within 180 days were included in Referent #1, but excluded from Referent #2 and #5.

2. Number of PIO varies due to exclusion of prevalent users of the drugs of interest in each new-user comparison

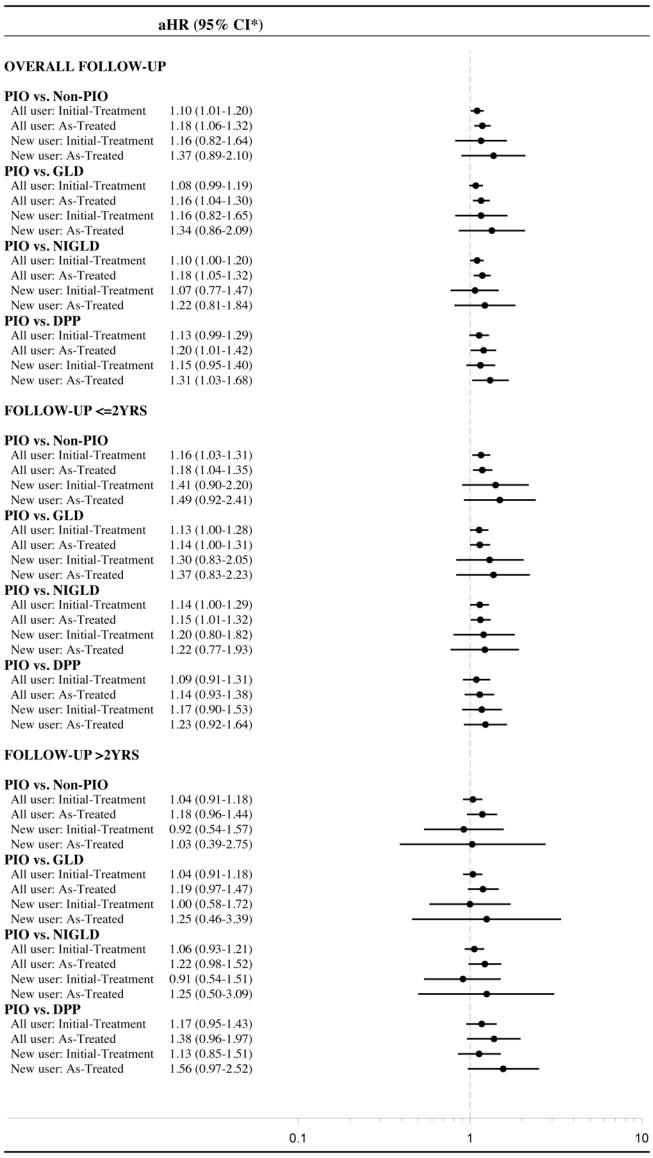

Figure 2.

Fully-adjusted hazard ratios for relative bladder cancer incidence rates among pioglitazone users and each referent obtained using the multivariate Cox proportional hazards model that included age, age-squared, male sex, race (black, other, ref: white), cohort entry year (2008, 2009, 2011, 2012, 2013, 2014, 2015, ref: 2010), smoking status, CHF, MI, stroke, prevalent cancer based on all available data, nephropathy, neuropathy, retinopathy, ACE, loop diuretics, statins, TZDs, DPP-4s, metformin, sulphonylureas, SGLT-2s, fast-acting insulin, long-acting insulin, other glucose-lowering drugs. ACE, angiotensin-converting enzyme inhibitor; CHF, congestive heart failure; CI, confidence interval; DPP, dipeptidyl-peptidase-4; GLD, glucose lowering drug; HR, hazard ratio; MI, myocardial infarction; NIGLD, noninsulin glucose-lowering drug; PIO, pioglitazone; TZD, thiazolidinedione.

Table 1.

Distribution (%) of patient characteristics among pioglitazone users & each referent - All User Cohorts

	PIO	Non-PIO	PIO	GLD	PIO	NIGLD	PIO	DPP
N	**135,188**	**1,375,024**	**135,188**	**828,527**	**135,188**	**705,446**	**135,188**	**128,089**
Demographics and Lifestyle at Cohort Entry								
Age, mean (SD)	74.7 (6.7)	75.9 (7.7)	74.7 (6.7)	74.9 (7.3)	74.7 (6.7)	74.8 (7.2)	74.7 (6.7)	75.2 (7.1)
Age, median (IQR)	73 (69,79)	74 (69,81)	73 (69,79)	73 (69,80)	73 (69,79)	73 (69,80)	73 (69,79)	74 (69,80)
Male	43.6	40.3	43.6	41.3	43.6	41.7	43.6	41.8
White	74.3	78.7	74.3	78.5	74.3	79.1	74.3	77.5
Black	11.7	12.4	11.7	12.8	11.7	11.9	11.7	11.3
Other Race †	14.0	8.9	14.0	8.7	14.0	9.1	14.0	11.2
Index Year: 2008	50.6	34.7	50.6	41.3	50.6	39.3	50.6	13.8
Index Year: 2009	12.1	9.1	12.1	7.3	12.1	7.6	12.1	7.4
Index Year: 2010	11.1	8.0	11.1	6.7	11.1	7.0	11.1	8.2
Index Year: 2011	8.2	8.4	8.2	7.3	8.2	7.6	8.2	11.6
Index Year: 2012	4.2	8.7	4.2	7.9	4.2	8.1	4.2	13.5
Index Year: 2013	4.1	9.4	4.1	8.8	4.1	9.1	4.1	14.8
Index Year: 2014	6.8	14.1	6.8	13.8	6.8	14.3	6.8	21.0
Index Year: 2015	2.9	7.7	2.9	6.9	2.9	7.0	2.9	9.7
Smoking ‡	7.7	12.3	7.7	11.4	7.7	11.1	7.7	13.1
Diabetic Complications								
Nephropathy	8.4	6.0	8.4	7.7	8.4	5.8	8.4	10.3
Neuropathy	19.5	13.3	19.5	18.0	19.5	15.9	19.5	22.6
Retinopathy	19.3	10.6	19.3	15.5	19.3	13.2	19.3	17.3
Diabetic Medication Use								
Thiazolidinediones	69.1	5.2	69.1	7.9	69.1	8.2	69.1	8.7
DPP-4	11.3	4.8	11.3	7.6	11.3	8.4	11.3	35.1
Metformin	57.3	29.6	57.3	46.9	57.3	52.8	57.3	62.5
Sulfonylureas	51.0	22.8	51.0	36.0	51.0	40.1	51.0	49.2
Other §	6.8	2.8	6.8	4.4	6.8	4.7	6.8	6.4
SGLT-2	0.2	0.1	0.2	0.1	0.2	0.2	0.2	0.4
Fast-Acting Insulin	6.9	8.2	6.9	12.4	6.9	7.4	6.9	8.4
Long-Acting Insulin	16.8	15.6	16.8	23.8	16.8	15.6	16.8	18.1
Other Co-morbidities								
CHF	15.6	23.0	15.6	21.8	15.6	18.8	15.6	23.0
COPD	14.1	19.9	14.1	18.0	14.1	16.7	14.1	17.7
MI	0.7	1.1	0.7	1.1	0.7	0.9	0.7	1.1
Stroke	10.0	12.9	10.0	11.9	10.0	10.6	10.0	11.8
History of Cancer ¶	16.5	20.7	16.5	17.9	16.5	18.0	16.5	21.7
Medication Use								
ACE	42.3	37.0	42.3	40.8	42.3	40.3	42.3	39.7

	PIO	Non-PIO	PIO	GLD	PIO	NIGLD	PIO	DPP
N	**135,188**	**1,375,024**	**135,188**	**828,527**	**135,188**	**705,446**	**135,188**	**128,089**
ARB	18.5	15.8	18.5	16.5	18.5	16.1	18.5	19.8
Beta Blockers	42.7	47.3	42.7	47.5	42.7	46.2	42.7	50.6
CCBs	29.1	31.3	29.1	31.0	29.1	30.1	29.1	32.4
Loop Diuretics	23.7	27.4	23.7	28.2	23.7	25.1	23.7	28.5
Statins	66.2	51.1	66.2	54.8	66.2	55.1	66.2	56.7

ACE, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blockers; CCB, Calcium Channel Blocker; CHF, Congestive Heart Failure; COPD, Chronic Obstructive Pulmonary Disease; DPP, dipeptidyl-peptidase-4; GLD, Glucose-Lowering Drug; IQR, interquartile range; NIGLD, Non-Insulin Glucose-Lowering Drug; PIO, pioglitazone; SD, Standard Deviation

† Other race combines the following races as defined by Medicare: Other, Asian, Hispanic, or Native American

‡ Smoking was defined using a validated algorithm that has nearly perfect specificity and PPV, but poor sensitivity (27.9% [95% CI: 16.6–39.1%])

§ Other diabetic medications included alpha-glucosidase inhibitors, amylin analogs, Glucagon-like peptide-1s, and meglitinides.

¶ History of cancer was evaluated during all available data prior to cohort entry.

Table 2.

Distribution (%) of patient characteristics among initiators of pioglitazone & each referent - New User Cohorts[†])

	PIO[‡]	Non-PIO	PIO[‡]	GLD	PIO[‡]	NIGLD	PIO[‡]	DPP
N	**5,752**	**675,986**	**5,752**	**172,663**	**7,547**	**174,512**	**33,551**	**76,503**
Demographics and Lifestyle at Cohort Entry								
Age, mean (SD)	75.4 (6.9)	76.8 (7.8)	75.4 (6.9)	75.2 (7.1)	75.4 (6.9)	75.0 (7.0)	74.9 (6.7)	75.7 (7.1)
Age, median (IQR)	74 (70,80)	76 (70,83)	74 (70,80)	74 (69,80)	74 (70,80)	73 (69,80)	74 (69,79)	74 (70,81)
Male	45.0	39.4	45.0	42.8	43.7	42.2	42.7	39.5
White	70.4	79.5	70.4	79.4	68.8	79.4	72.5	76.7
Black	11.8	11.3	11.8	11.2	14.0	11.1	11.7	11.1
Other Race[§]	17.8	9.2	17.8	9.5	17.2	9.6	15.9	12.3
Index Year: 2008	26.5	20.3	26.5	12.8	26.0	12.6	23.2	7.7
Index Year: 2009	22.3	12.7	22.3	13.9	22.7	13.8	24.1	9.0
Index Year: 2010	16.2	11.1	16.2	12.9	16.9	12.8	19.4	10.1
Index Year: 2011	11.0	11.0	11.0	12.4	11.1	12.5	11.6	14.2
Index Year: 2012	4.9	10.6	4.9	11.8	4.9	12.0	4.6	15.8
Index Year: 2013	5.4	11.1	5.4	11.9	5.6	12.2	5.7	15.9
Index Year: 2014	5.9	14.0	5.9	13.0	5.9	13.6	6.7	17.2
Index Year: 2015	7.7	9.3	7.7	11.3	6.9	10.6	4.6	10.2
Smoking[¶]	9.2	13.5	9.2	13.7	9.4	13.4	9.0	13.8
Diabetic Complications								
Nephropathy	5.8	2.8	5.8	3.8	8.9	4.4	8.5	10.2
Neuropathy	10.1	5.5	10.1	8.3	16.0	10.4	19.3	22.6
Retinopathy	8.0	3.0	8.0	5.2	13.3	7.2	16.6	16.3
Diabetic Medication Use								
Thiazolidinediones	--	--	--	--	--	--	--	--
DPP-4	--	--	--	--	--	--	--	--
Metformin	--	--	--	--	--	--	60.3	61.7
Sulfonylureas	--	--	--	--	--	--	53.4	49.6
Other [††]	--	--	--	--	--	--	5.4	5.6
SGLT-2	--	--	--	--	--	--	0.2	0.2
Fast-Acting Insulin	--	--	--	--	13.3	8.2	8.2	9.1
Long-Acting Insulin	--	--	--	--	25.1	13.3	16.3	17.4
Other Co-morbidities								
CHF	15.0	22.9	15.0	20.5	19.1	20.0	16.7	24.9
COPD	16.9	21.7	16.9	20.0	18.8	19.4	15.8	19.4
MI	0.8	1.2	0.8	1.1	0.8	1.1	0.8	1.2
Stroke	10.6	13.5	10.6	12.1	12.6	11.6	11.4	12.9
History of Cancer [‡‡]	18.8	24.4	18.8	22.4	19.6	22.2	19.8	24.2
Medication Use								

	PIO‡	Non-PIO	PIO‡	GLD	PIO‡	NIGLD	PIO‡	DPP
N	**5,752**	**675,986**	**5,752**	**172,663**	**7,547**	**174,512**	**33,551**	**76,503**
ACE	29.4	30.5	29.4	31.9	32.5	33.2	42.2	40.3
ARB	15.0	14.2	15.0	13.5	15.8	14.1	16.7	19.3
Beta Blockers	40.9	46.4	40.9	45.9	43.3	46.5	44.8	51.7
CCBs	28.9	31.5	28.9	30.6	31.0	30.7	31.7	34.0
Loop Diuretics	19.7	25.0	19.7	24.3	25.0	25.0	22.1	29.5
Statins	50.3	45.5	50.3	46.9	51.7	48.3	59.6	55.5

ACE, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blockers; CCB, Calcium Channel Blocker; CHF, Congestive Heart Failure; COPD, Chronic Obstructive Pulmonary Disease; DPP, dipeptidyl-peptidase-4; GLD, Glucose-Lowering Drug; IQR, interquartile range; NIGLD, Non-Insulin Glucose-Lowering Drug; PIO, pioglitazone; SD, Standard Deviation

†New use of GLD exposure was determined based on no prescription claims for the drug classes included in each comparison during the 365-day period prior to the initial claim.

‡Number of people initiating PIO differs for each comparison due to exclusions of prior use of drugs included in comparison only.

§Other race combines the following races as defined by Medicare: Other, Asian, Hispanic, or Native American

¶Smoking was defined using a validated algorithm that has nearly perfect specificity and PPV, but poor sensitivity (27.9% [95% CI: 16.6–39.1%])

††Other diabetic medications included alpha-glucosidase inhibitors, amylin analogs, Glucagon-like peptide-1s, and meglitinides.

‡‡History of cancer was evaluated during all available data prior to cohort entry